Crotalus oreganus concolor: Envenomation Case with Venom Analysis, and a Diagnostic Conundrum of Myo-neurological Symptoms

Short Title: *Crotalus oreganus concolor* Envenomation

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Abstract

A case of Midget-faded Rattlesnake (*Crotalus oreganus concolor*) envenoming to an adult male professional herpetologist occurred in a rural setting and resulted in what appeared as an array of venom induced myo-neurological symptoms. The patient experienced blurry vision, total body paresthesia, dyspnea, chest tightness, and waves of spastic muscle movements of the hands and feet that appeared like tetany. These symptoms were confounding as to whether they were potentially venom induced or were related to stress-induced physiological responses. Local envenomation effects were minimal, and coagulation parameters remained within normal limits. Antivenom was not administered per patient concerns related to a prior history of acute allergic reactions to antivenom. Venom was collected from the *C. o. concolor* responsible for the bite, and analysis revealed the presence of high levels of myotoxins (SR calcium pump antagonists), and concolor toxin, a presynaptic neurotoxin that can cause myotoxic effects and respiratory paralysis; several serine proteinases associated with coagulopathies were also present in the venom profile.

Key words: rattlesnake, snakebite, hyperventilation, carpopedal, alkalemia, hypocalcemia

Introduction

The Midget-faded Rattlesnake (*Crotalus oreganus concolor*) is an uncommon, small (50-65 cm total body length) subspecies originally assigned to the *Crotalus viridis* complex, and currently recognized as a subspecies in the *Crotalus oreganus* clade.[1-2] It is indigenous to a restricted geographic range of the Colorado Plateau that includes west-central Colorado, the Colorado and Green River basins, eastern Utah, southwestern Wyoming, and extreme northern Arizona.[3,4,5]

Crotalus o. concolor venom studies have revealed the presence of a potent lethal toxin, antigenically similar to Mojave toxin.[6-7] It has been determined to be one of the most lethal crotaline venoms, nearly equal in toxicity to *Crotalus durissus terrificus* and *Crotalus scutulatus scutulatus* venoms, based on murine lethality experiments.[8] Additionally, it has been reported that *C. o. concolor* venom lethality ranges from 10-30 fold greater than multiple other crotaline species.[8-9] A presynaptic phospholipase A_2-ß-neurotoxin (concolor toxin) and nonenzymatic peptide myotoxins have been identified as major venom components.[9-12]

Envenoming of humans by *C. o. concolor* is rare, and the case reported here illustrates what clinically appeared to be possible venom induced myo-neurological symptoms that were confounded in interpretation by physiological stresses. Analysis of venom from the *C. o. concolor* responsible in this case suggested a possible correlation between specific venom components and several observed clinical symptoms.

Case Presentation

A healthy 61-y-old male, professional herpetologist sustained a bite from a captive (wild caught) adult male *C. o. concolor* (Figure 1 A). Patient history included prior crotaline envenomings from *Crotalus horridus*, *C. h. atricaudatus* (subspecies recognized at the time of the bite) and *Crotalus durissus ruruima*. Treatments involved Wyeth anticrotalic antivenoms and Instituto

Butantan anticrotalico, with anaphylactic reactions having occurred. Patient medication history included migraine headache prescriptions (rizatriptan, atenolol, and amitriptyline).

The incident took place in a remote facility, and the bite occurred as the snake was being removed from a drawer-type housing unit, resulting in a single fang puncture into the right thumb (Figure 1 B). Immediately, the patient experienced generalized "pins and needles" sensations in the bitten thumb that rapidly progressed to pain, followed by tingling of the lips, and feeling chest tightness. Within 15 min the patient reported total body tingling. The first responder found the patient resting supine on the floor, and reported the patient did not appear anxious or agitated, with no obvious signs of hyperventilation (20 breaths min^{-1}). The patient described feeling like he was "wearing a clay mask and a hat with hat band one size too small constricting around my forehead". The affected limb was splinted for immobilization during a 1 h ground ambulance transport to the helispot, and subsequent 45 min helicopter flight to a rural hospital. During ground transport the patient complained of breathing difficulty, and supplemental oxygen was provided via nasal cannula. Tightening of the tongue, blurred vision, and difficulty speaking were also experienced. Three distinct waves of transient neuromuscular spasms associated with inspirational weakness ensued. Spastic simultaneous contractures of first the left hand, and 2^{nd} to a lesser degree the right (bitten) hand and foot/toes, followed by a 3^{rd} wave that involved the left forearm, lower leg and foot. The first responder described these waves as severe spastic muscle movement, tetany like (Figure 2 A). The patient was alert and oriented; blood pressure was normal by sphygmomanometer/cuff (113/72 mm Hg), and pulse normal by palpitation (69 beats min^{-1}) (Figure 2 B).

Approximately 2 1/2 h postbite the patient arrived to the emergency department, and the myo-neurological symptoms had abated. Examination revealed a single fang puncture in the

distal phalangeal region of the right thumb and swelling that extended proximally to the thenar eminence. Chemistry panel, complete blood count, electrolytes, coagulation and hematological parameters were within normal limits excepting a slightly elevated D-dimer (566 ng mL^{-1} FEU; reference lab range 190-490 ng mL^{-1} FEU), and elevated creatine kinase (CK) 3394 U L^{-1} (reference lab range 22-198 U L^{-1}). Over the following 24 h there was a small decline in total serum calcium from 8.8 mg dL^{-1} (3 h) to 7.7 mg dL^{-1} (22 h) (reference lab range 8.5-10.1 mg dL^{-1}), and a corresponding slight decline in serum albumin from 4.2 g dL^{-1} (3 h) to 3.5 g dL^{-1} (22 h) (reference lab range 3.4-5.0 g dL^{-1}). There was no evidence of bleeding at any time. Swelling spread proximally to mid-forearm over the first 3 h, but local pain had lessened. Medical staff observed patient total body strength weakness with poor coordination, requiring walking frame assistance. There was no evidence of compartment syndrome. Despite indications for antivenom its administration was declined by the patient because of anaphylactic reactions from previous antivenom treatments. The patient was observed for another 6 h and discharged at 25 h postbite (22 h post admission) in stable condition. At 24 h after discharge the patient remained weak, but could walk without assistance. Myalgia in the right arm and generalized weakness persisted for several days. At 3 weeks follow-up the bitten thumb skin sloughed, thumb numbness persisted, but other local symptoms had resolved completely, and all laboratory studies were unremarkable. Venom from the offending *C. o. concolor* was collected for assay and analysis of venom components and their potential correlation to observed symptoms.

Methods - Venom Analysis

Venom was extracted manually from the *C. o. concolor* responsible for the bite approximately 4 days after the bite, centrifuged to pellet the cell debris, and the supernatant lyophilized (fluid yield 120 µL; ≈ 27 mg dry venom). Lyophilized venom was solubilized in PBS (8.0 mg mL^{-1}),

and 200 µL (1.6 mg) was subjected to reversed phase high performance liquid chromatography (RP-HPLC) as reported previously; 1 min fractions were collected and lyophilized.[13] Toxins were identified from the known elution profiles of purified toxins and quantified via peak area integration (% total area).

HPLC fractions were also subjected to polyacrylamide gel electrophoresis (SDS-PAGE) under reducing conditions to identify chromatogram peaks.[13] Crude venom was assayed for protein content via Pierce BCA assay, and then for 6 enzyme activities common to rattlesnake venoms.[10,14] These data were used in conjunction with HPLC chromatogram data to identify protein families present and their relative abundance in the venom.

Discussion and Results

Our patient's symptoms illustrate a potential diagnostic conundrum clinicians may face in cases of snakebite envenoming: what symptoms might be venom induced effects, and what symptoms might be related to stress induced physiological responses? Our patient experienced generalized paresthesia, blurred vision, waves of spastic tetany like symptoms of the hands and feet (carpopedal spasms), breathing difficulties, numbness, and generalized weakness that persisted for days, all symptoms consistent with venom induced effects reported in other cases of North American rattlesnake envenoming, including *C. o. concolor*.[9,15,16,17] However, in our patient the tetany like carpopedal spasms may not have been venom induced, but likely from patient anxiety induced hyperventilation, or triggered by sphygmomanometer cuff inflation.[18-19] *Crotalus o. concolor* venom contains myotoxic and neurotoxic components capable of eliciting neurotoxic symptoms.[9-10,12] Purified *C. o. concolor* venom toxins injected into mice elicit myotoxic effects of rapid ataxia, hind limb extension, and respiratory distress.[7,20] Collectively, symptoms in the

presented case combined with the interpretation of the inflicting snake's venom analysis provides for interesting discussion.

Venomous snakebite can trigger significant anxiety leading to an autonomic response of hyperventilation-induced alkalemia with consequent precipitation of hypocalcemia resulting in symptoms of breathlessness and paresthesia of the face and hands, yet blood pressure remains normal.[18] Tetany like symptoms of painful sharp involuntary flexion of the wrist and ankle joints (carpopedal spasms), cramps, and muscle twitching may be clinically misleading. These physiological responses are due to decreased extracellular ionized calcium resulting in a hyperexcitability state of muscles and nerves.[18] Ionized serum calcium was not measured in our patient; however, the patient was not observed to be tachypnic, though hyperventilation may occur via slow deep breathing. Hypocalcemic tetany of the lower extremities has been reported in a case of *Crotalus scutulatus* envenoming with minimal coagulopathy, but was thought to have been subsequent to rhabdomyolysis.[21] Our patient had a normal blood pressure and may have deeply hyperventilated to the point of respiratory alkalosis followed by hypocalcemic tetany. The carpopedal symptoms fit the profile of stress related physiological responses, which were considered a contributing root of cause.

Blood pressure measurement via sphygmomanometer with an inflatable cuff was used for monitoring our patient's blood pressure during ambulance transport. Cuff inflation, in conjunction with hyperventilation induced hypocalcemia, likely triggered a classic Trousseau sign.[19] Cuff inflation to greater than the mean arterial pressure can result in the hand adopting a posture of metacarpophalangeal joint flexion, and the interphalangeal joints of the fingers and thumb extended so that the thumb is in an opposing posture, as observed in our patient (Figure 2B). This phenomenon has been reported in 1-4% of healthy individuals, but has not been

reported to be associated with cases of snakebite envenoming.[19] Although *C. o. concolor* myotoxic venom components can induce muscle contractile activity, causing rapid tetany like hind limb hyperextension in mice, a symptom somewhat similar to the extension of the ankles, feet, and toes as observed in our patient, this symptom was likely a stress induced response rather than venom induced [20,22]

Our patient's other myo-neurological symptoms of paresthesia, respiratory distress, and total body weakness may possibly have been related to the high myotoxin content and concolor toxin in the *C. o. concolor's* venom (Figure 3, Table 2). Studies in mice injected with *C. o. concolor* venom showed they died from rapid respiratory failure, suggesting that venom possibly may have contributed to our patient's respiratory difficulty, as has been reported to occur following *C. scutulatus, C. cerastes, C. oreganus helleri,* and *C. horridus* envenomations.[16-17,23-24]

Venom was delivered to our patient via a single fang puncture, and it is reasonable to assume it was not a maximum dose and a potential reason for the reduced severity and duration of envenoming symptoms. Neurotoxic effect duration following snake envenoming is highly variable.[25]. The short duration of myo-neurological actions in our patient may possibly have been related to dose-dependent pharmacokinetics or pharmacokinetic metabolic actions on a responsible toxin.

Myokymia has been reported following envenoming by *C. o. concolor* and other North American rattlesnakes.[15,26-27] In our patient, the periodic episodes of tetany like, carpopedal spasms were distinctly different than myokymia or fasciculations.[15,27]

Crotaline envenomation can result in hematological effects ranging from mild to severe coagulopathy, and neurologically from paresthesia to seizures, and coma. Consequently, patients

can exhibit multiple combinations of clinical manifestations varying in severity. [28] Thus, the absence of hematological effects in our patient, in the presence of neurological symptoms, was not uncharacteristic of rattlesnake envenoming. Neurological symptoms following *C. cerastes* and *C. concolor* envenoming, without hematological effects, have been reported.[9,15-17]

Local wound complications in our patient were modest, including ecchymosis, swelling, pain, and skin sloughing. Elevated creatine kinase (CK), a routinely used marker for tissue damage and myonecrosis, has been reported in 2 cases of *C. o. concolor* envenoming (ranging from 1800 – 17,000 IU L^{-1}), and in the absence of coagulopathic complications.[15,29] Our patient's elevated CK value (3394 U L^{-1}) at 22 h post envenoming was indicative of venom induced local tissue/muscle damage to the bitten thumb.

Medications may potentially influence snake envenoming symptoms, and our patient's medications (atenolol, rizatriptan, and amitriptyline) have reported adverse effects of blurred vision, numbness, chest tightness, paresthesia, and weakness similar to our patient's symptoms.[30-31] Our patient reported having no adverse effects to these medications prior to the bite, suggesting drug/venom interactions were noncontributory to observed symptoms.

Venom analyses from the responsible snake revealed abundant PLA_2-based ß neurotoxin (concolor toxin), and nonenzymatic peptide myotoxins.[9,12,32] Enzyme analyses revealed the presence of 6 enzymes common to rattlesnake venoms (Table 1); however, their levels varied significantly from averaged values based on 22 taxa of rattlesnakes.[33] Notably, snake venom metalloproteinase activity (SVMP; azocasein metalloproteinase) was barely detectable, and this likely was responsible for the lack of hemorrhage, rhabdomyolysis or inflammation. These very low levels of SVMPs are characteristic of type II venoms, including that of *C. o. concolor*.[10] Thrombin-like and kallikrein-like serine proteinase activities in the venom were quite high, and

thrombin-like activity was nearly twice the average value of many rattlesnake venoms. Because of these high activity levels coagulopathies including hypofibrinogenemia would have been expected; however, lab blood panels did not indicate any form of coagulopathy. Phospholipase A_2 levels were moderate, but not noteworthy compared to other species; PLA_2 activity is sometimes associated with severe inflammation, myotoxicity, and occasionally renal damage/failure. The lack of these symptoms indicates that this acidic PLA_2 was not particularly toxic, consistent with similar enzymatic PLA_2s from other species.

RP-HPLC analysis of the venom (Figure 3) indicated the presence of myotoxins I & II, small peptide components common to the venoms of numerous species of rattlesnakes.[31] In humans, they may be responsible for fasciculations [possibly muscle weakness, both acute and prolonged].[25] The myotoxin content of this venom was extremely high and comprised > 59% of the total venom proteins; concolor toxin made up > 21% of the venom total protein content (Figure 3, Table 2). The combined actions of these two protein families, comprising >80% of venom proteins, possibly contributed to the rapid paraesthesias and other tetany like symptoms observed in the patient.

Conclusions

The case reported here is an interesting academic case in that certain symptoms, similar to previously reported *C. o. concolor* cases of envenoming, were potentially a hybridization of anxiety and stress induced symptoms integrated with venom induced symptoms. Analyses of ionized calcium, arterial blood gases, and a formal patient neurological evaluation would have provided for a more comprehensive assessment for confirming or ruling out the source of some symptoms. Although the venom profile of the snake involved showed a high myotoxin content their role in the myo-neurological (carpopedal spasms) symptoms is unlikely. Thus, the

presented case illustrates a diagnostic conundrum, and medical personnel should be cognizant of the potential for confounding symptoms associated with rattlesnake envenoming, and interpretation as to their cause.

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Author Contributions

Acquisition of case data; analysis of case data: (DEK), (MO), (VS), (JG)

Photo credits: Figure 1 (DEK), Figure 2 (JG)

Drafting of case and overall manuscript: (DEK)

Acquisition of venom data; analysis of venom data: (SPM), (CFS)

Drafting venom analysis portion of manuscript: (SPM), (CFS)

Critical revision and approval of final manuscript: (DEK), (SPM)

Conflicts of Interest

The authors declare no conflict of interest, and external financial support - NONE.

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Figure Legends

Figure 1. Panel A: The midget faded rattlesnake (*Crotalus oreganus concolor*) responsible for the bite, in its housing drawer enclosure from which it struck, imparting a single fang puncture to the patient. Panel B: Single fang puncture into the distal phalangeal region of the right thumb.

Figure 2. Panel A: Tetany-like spasms showing flexion of the hands and extension of the feet (carpopedal spasms) that began 30 min post bite. Three waves of approximately 10 min each, 20 min apart, were observed. Panel B: Blood pressure and pulse were normal to low as measured by palpitation and the sphygmomanometer/cuff placed on the contralateral arm.

Figure 3. RP-HPLC chromatogram of *Crotalus oreganus concolor* venom, 1.6 mg in 200 µL PBS. Identification of peaks are based on SDS-PAGE and enzyme activity assays. Inset: reducing SDS-PAGE of indicated HPLC fractions. CRiSP, cysteine-rich secretory protein.


A


B


A


B

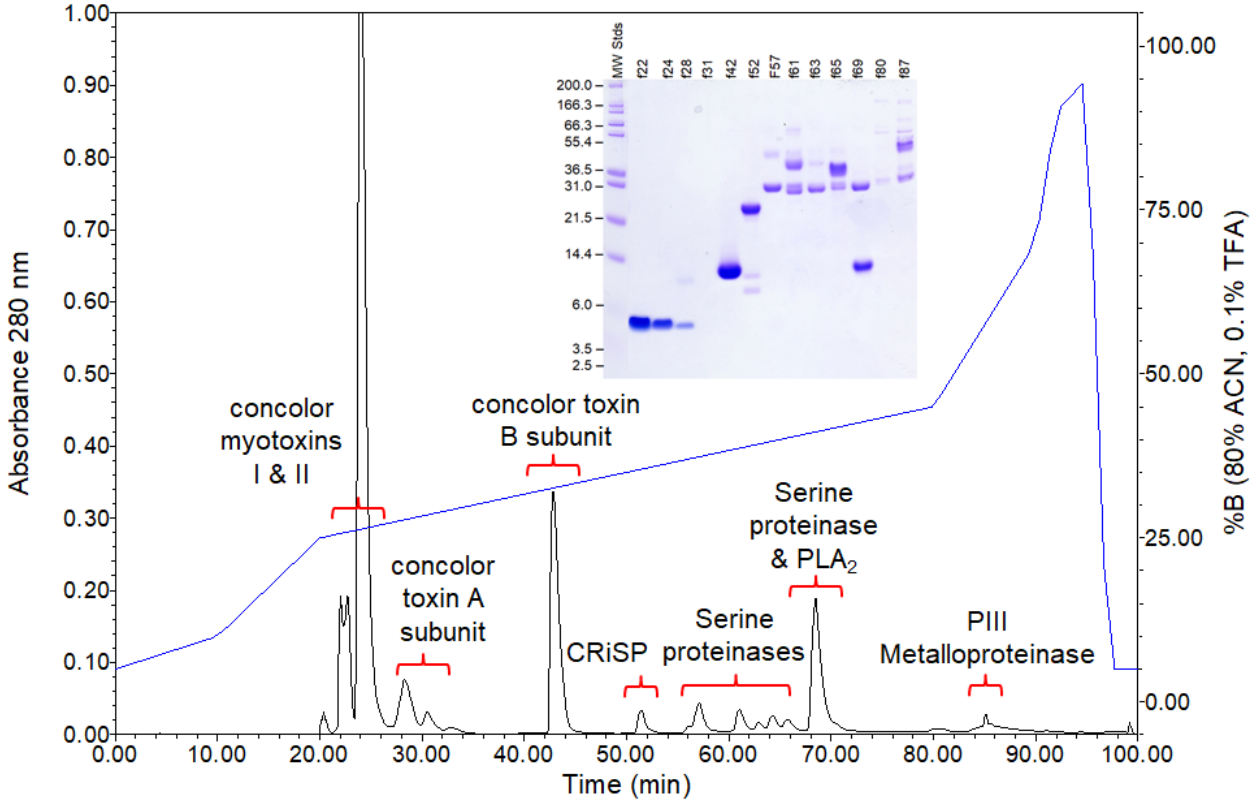

Table 1. Assays of *Crotalus o. concolor* venom for enzyme activities common to rattlesnake venoms. Activity levels in the offending venom relative to averages of 22 taxa of rattlesnakes (Mackessy, 2008) are also indicated.

Enzyme Assayed	Specific Activity	Relative Activity
Phospholipase A_2 (nmol product/min/mg)	25.4	↓
Azocasein metalloproteinase (Abs 342nm/min/mg)	0.01	↓ ↓
Kallikrein-like (nmol product/min/mg)	971	↑ ↑
Thrombin-like (nmol product/min/mg)	1389	↑ ↑
Phosphodiesterase (Abs 400nm/min/mg)	1.0	↑

L-amino acid oxidase (nmol product/min/mg)	9.7	↓

↓, venom activity lower than average; ↑, venom activity higher than average